

COMBIVIR[®]
(lamivudine/zidovudine)
Tablets

WARNING

ZIDOVUDINE, ONE OF THE TWO ACTIVE INGREDIENTS IN COMBIVIR, HAS BEEN ASSOCIATED WITH HEMATOLOGIC TOXICITY INCLUDING NEUTROPENIA AND SEVERE ANEMIA, PARTICULARLY IN PATIENTS WITH ADVANCED HIV DISEASE (SEE WARNINGS). PROLONGED USE OF ZIDOVUDINE HAS BEEN ASSOCIATED WITH SYMPTOMATIC MYOPATHY.

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION, INCLUDING LAMIVUDINE, ZIDOVUDINE, AND OTHER ANTIRETROVIRALS (SEE WARNINGS).

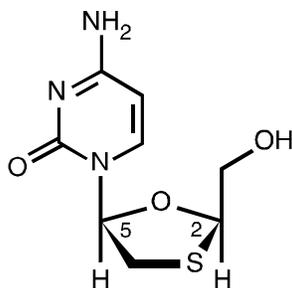
SEVERE ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED IN PATIENTS WHO ARE CO-INFECTED WITH HEPATITIS B VIRUS (HBV) AND HIV AND HAVE DISCONTINUED LAMIVUDINE, WHICH IS ONE COMPONENT OF COMBIVIR. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO DISCONTINUE COMBIVIR AND ARE CO-INFECTED WITH HIV AND HBV. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE WARNINGS).

DESCRIPTION

COMBIVIR: COMBIVIR Tablets are combination tablets containing lamivudine and zidovudine. Lamivudine (EPIVIR[®], 3TC[®]) and zidovudine (RETROVIR[®], azidothymidine, AZT, or ZDV) are synthetic nucleoside analogues with activity against human immunodeficiency virus (HIV).

COMBIVIR Tablets are for oral administration. Each film-coated tablet contains 150 mg of lamivudine, 300 mg of zidovudine, and the inactive ingredients colloidal silicon dioxide, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, and titanium dioxide.

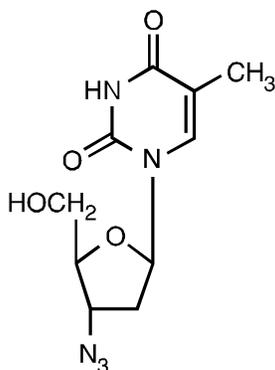
Lamivudine: The chemical name of lamivudine is (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one. Lamivudine is the (-)-enantiomer of a dideoxy analogue of cytidine. Lamivudine has also been referred to as (-)-2',3'-dideoxy, 3'-thiacytidine. It has a molecular formula of C₈H₁₁N₃O₃S and a molecular weight of 229.3. It has the following structural formula:



40
41
42
43
44
45
46
47

Lamivudine is a white to off-white crystalline solid with a solubility of approximately 70 mg/mL in water at 20°C.

Zidovudine: The chemical name of zidovudine is 3'-azido-3'-deoxythymidine. It has a molecular formula of C₁₀H₁₃N₅O₄ and a molecular weight of 267.24. It has the following structural formula:



48
49
50

Zidovudine is a white to beige, odorless, crystalline solid with a solubility of 20.1 mg/mL in water at 25°C.

51 MICROBIOLOGY

52 **Mechanism of Action: Lamivudine:** Lamivudine is a synthetic nucleoside analogue.
53 Intracellularly, lamivudine is phosphorylated to its active 5'-triphosphate metabolite, lamivudine
54 triphosphate (L-TP). The principal mode of action of L-TP is inhibition of reverse transcriptase
55 (RT) via DNA chain termination after incorporation of the nucleoside analogue. L-TP is a weak
56 inhibitor of mammalian DNA polymerases α and β , and mitochondrial DNA polymerase- γ .

57 **Zidovudine:** Zidovudine is a synthetic nucleoside analogue. Intracellularly, zidovudine is
58 phosphorylated to its active 5'-triphosphate metabolite, zidovudine triphosphate (ZDV-TP). The
59 principal mode of action of ZDV-TP is inhibition of RT via DNA chain termination after
60 incorporation of the nucleoside analogue. ZDV-TP is a weak inhibitor of the mammalian DNA
61 polymerase- α and mitochondrial DNA polymerase- γ and has been reported to be incorporated
62 into the DNA of cells in culture.

63 **Antiviral Activity In Vitro:** The relationship between in vitro susceptibility of HIV to
64 lamivudine or zidovudine and the inhibition of HIV replication in humans has not been
65 established.

66 **Lamivudine Plus Zidovudine:** In HIV-1-infected MT-4 cells, lamivudine in combination
67 with zidovudine had synergistic antiretroviral activity. Synergistic activity of lamivudine and
68 zidovudine was also shown in a variable-ratio study.

69 **Lamivudine:** In vitro activity of lamivudine against HIV-1 was assessed in a number of cell
70 lines (including monocytes and fresh human peripheral blood lymphocytes). IC₅₀ and IC₉₀ values
71 (50% and 90% inhibitory concentrations) for lamivudine were 0.0006 mcg/mL to 0.034 mcg/mL
72 and 0.015 to 0.321 mcg/mL, respectively. Lamivudine had anti-HIV-1 activity in all acute
73 virus-cell infections tested.

74 **Zidovudine:** In vitro activity of zidovudine against HIV-1 was assessed in a number of cell
75 lines (including monocytes and fresh human peripheral blood lymphocytes). The IC₅₀ and IC₉₀
76 values for zidovudine were 0.003 to 0.013 mcg/mL and 0.03 to 0.13 mcg/mL, respectively.
77 Zidovudine had anti-HIV-1 activity in all acute virus-cell infections tested. However, zidovudine
78 activity was substantially less in chronically infected cell lines. In cell culture drug combination
79 studies with zidovudine, interferon-alpha demonstrated additive activity and zalcitabine,
80 didanosine, saquinavir, indinavir, ritonavir, nelfinavir, nevirapine, and delavirdine demonstrated
81 synergistic activity.

82 **Drug Resistance: Lamivudine Plus Zidovudine Administered As Separate**
83 **Formulations:** In patients receiving lamivudine monotherapy or combination therapy with
84 lamivudine plus zidovudine, HIV-1 isolates from most patients became phenotypically and
85 genotypically resistant to lamivudine within 12 weeks. In some patients harboring
86 zidovudine-resistant virus at baseline, phenotypic sensitivity to zidovudine was restored by
87 12 weeks of treatment with lamivudine and zidovudine. Combination therapy with lamivudine
88 plus zidovudine delayed the emergence of mutations conferring resistance to zidovudine.

89 HIV-1 strains resistant to both lamivudine and zidovudine have been isolated from patients
90 after prolonged lamivudine/zidovudine therapy. Dual resistance required the presence of multiple
91 mutations, the most essential of which may be at codon 333 (Gly→Glu). The incidence of dual
92 resistance and the duration of combination therapy required before dual resistance occurs are
93 unknown.

94 **Lamivudine:** Lamivudine-resistant isolates of HIV-1 have been selected in vitro and have
95 also been recovered from patients treated with lamivudine or lamivudine plus zidovudine.
96 Genotypic analysis of the resistant isolates showed that the resistance was due to mutations in the
97 HIV-1 reverse transcriptase gene at codon 184 from methionine to either isoleucine or valine.

98 **Zidovudine:** HIV isolates with reduced susceptibility to zidovudine have been selected in
99 vitro and were also recovered from patients treated with zidovudine. Genotypic analyses of the
100 isolates showed mutations which result in 5 amino acid substitutions (Met41→Leu,
101 Asp67→Asn, Lys70→Arg, Thr215→Tyr or Phe, and Lys219→Gln) in the HIV-1 reverse
102 transcriptase gene. In general, higher levels of resistance were associated with greater number of
103 mutations.

104 **Cross-Resistance:** Cross-resistance among certain reverse transcriptase inhibitors has been
105 recognized.

106 **Lamivudine Plus Zidovudine:** Cross-resistance between lamivudine and zidovudine
107 has not been reported. In some patients treated with lamivudine alone or in combination with
108 zidovudine, isolates have emerged with a mutation at codon 184, which confers resistance to
109 lamivudine. In the presence of the 184 mutation, cross-resistance to didanosine and zalcitabine
110 has been seen in some patients; the clinical significance is unknown. In some patients treated
111 with zidovudine plus didanosine or zalcitabine, isolates resistant to multiple drugs, including
112 lamivudine, have emerged (see under Zidovudine below).

113 **Lamivudine:** See Lamivudine Plus Zidovudine (above).

114 **Zidovudine:** HIV isolates with multidrug resistance to zidovudine, didanosine,
115 zalcitabine, stavudine, and lamivudine were recovered from a small number of patients treated
116 for ≥ 1 year with zidovudine plus didanosine or zidovudine plus zalcitabine. The pattern of
117 genotypic resistant mutations with such combination therapies was different (Ala62 \rightarrow Val,
118 Val75 \rightarrow Ile, Phe77 \rightarrow Leu, Phe116 \rightarrow Tyr, and Gln151 \rightarrow Met) from the pattern with zidovudine
119 monotherapy, with the 151 mutation being most commonly associated with multidrug resistance.
120 The mutation at codon 151 in combination with the mutations at 62, 75, 77, and 116 results in a
121 virus with reduced susceptibility to zidovudine, didanosine, zalcitabine, stavudine, and
122 lamivudine.

123 Multiple-drug resistance has been observed in 2 of 39 (5%) patients receiving zidovudine and
124 didanosine combination therapy for 2 years.

125 **CLINICAL PHARMACOLOGY**

126 **Pharmacokinetics in Adults: COMBIVIR:** One COMBIVIR Tablet was bioequivalent to
127 one EPIVIR Tablet (150 mg) plus one RETROVIR Tablet (300 mg) following single-dose
128 administration to fasting healthy subjects (n = 24).

129 **Lamivudine:** The pharmacokinetic properties of lamivudine in fasting patients are
130 summarized in Table 1. Following oral administration, lamivudine is rapidly absorbed and
131 extensively distributed. Binding to plasma protein is low. Approximately 70% of an intravenous
132 dose of lamivudine is recovered as unchanged drug in the urine. Metabolism of lamivudine is a
133 minor route of elimination. In humans, the only known metabolite is the trans-sulfoxide
134 metabolite (approximately 5% of an oral dose after 12 hours).

135 **Zidovudine:** The pharmacokinetic properties of zidovudine in fasting patients are
136 summarized in Table 1. Following oral administration, zidovudine is rapidly absorbed and
137 extensively distributed. Binding to plasma protein is low. Zidovudine is eliminated primarily by
138 hepatic metabolism. The major metabolite of zidovudine is 3'-azido-3'-deoxy-5'-O- β -D-
139 glucopyranuronosylthymidine (GZDV). GZDV area under the curve (AUC) is about 3-fold
140 greater than the zidovudine AUC. Urinary recovery of zidovudine and GZDV accounts for 14%
141 and 74% of the dose following oral administration, respectively. A second metabolite, 3'-amino-
142 3'-deoxythymidine (AMT), has been identified in plasma. The AMT AUC was one fifth of the
143 zidovudine AUC.

144

145 **Table 1. Pharmacokinetic Parameters* for Lamivudine and Zidovudine in Adults**

Parameter	Lamivudine		Zidovudine	
Oral bioavailability (%)	86 ± 16	n = 12	64 ± 10	n = 5
Apparent volume of distribution (L/kg)	1.3 ± 0.4	n = 20	1.6 ± 0.6	n = 8
Plasma protein binding (%)	<36		<38	
CSF:plasma ratio [†]	0.12 [0.04 to 0.47]	n = 38 [‡]	0.60 [0.04 to 2.62]	n = 39 [§]
Systemic clearance (L/hr/kg)	0.33 ± 0.06	n = 20	1.6 ± 0.6	n = 6
Renal clearance (L/hr/kg)	0.22 ± 0.06	n = 20	0.34 ± 0.05	n = 9
Elimination half-life (hr)	5 to 7		0.5 to 3	

146 * Data presented as mean ± standard deviation except where noted.

147 † Median [range].

148 ‡ Children.

149 § Adults.

150 || Approximate range.

151

152 **Effect of Food on Absorption of COMBIVIR:** COMBIVIR may be administered with or
 153 without food. The extent of lamivudine and zidovudine absorption (AUC) following
 154 administration of COMBIVIR with food was similar when compared to fasting healthy subjects
 155 (n = 24).

156 **Special Populations: Impaired Renal Function: COMBIVIR:** Because lamivudine and
 157 zidovudine require dose adjustment in the presence of renal insufficiency, COMBIVIR is not
 158 recommended for patients with impaired renal function (see PRECAUTIONS).

159 **Impaired Hepatic Function: COMBIVIR:** A reduction in the daily dose of zidovudine
 160 may be necessary in patients with mild to moderate impaired hepatic function or liver cirrhosis.
 161 Because COMBIVIR is a fixed-dose combination that cannot be adjusted for this patient
 162 population, COMBIVIR is not recommended for patients with impaired hepatic function.

163 **Pregnancy:** See PRECAUTIONS: Pregnancy.

164 **COMBIVIR:** No data are available.

165 **Zidovudine:** Zidovudine pharmacokinetics has been studied in a Phase 1 study of
 166 8 women during the last trimester of pregnancy. As pregnancy progressed, there was no evidence
 167 of drug accumulation. The pharmacokinetics of zidovudine was similar to that of nonpregnant
 168 adults. Consistent with passive transmission of the drug across the placenta, zidovudine
 169 concentrations in neonatal plasma at birth were essentially equal to those in maternal plasma at
 170 delivery. Although data are limited, methadone maintenance therapy in 5 pregnant women did
 171 not appear to alter zidovudine pharmacokinetics. In a nonpregnant adult population, a potential
 172 for interaction has been identified (see CLINICAL PHARMACOLOGY: Drug Interactions).

173 **Nursing Mothers:** See PRECAUTIONS: Nursing Mothers.

174 **Lamivudine:** Samples of breast milk obtained from 20 mothers receiving lamivudine
 175 monotherapy (300 mg twice daily) or combination therapy (150 mg lamivudine twice daily and
 176 300 mg zidovudine twice daily) had measurable concentrations of lamivudine.

177 **COMBIVIR:** No data are available.

178 **Zidovudine:** After administration of a single dose of 200 mg zidovudine to 13 HIV-
 179 infected women, the mean concentration of zidovudine was similar in human milk and serum.

180 **Pediatric Patients: COMBIVIR:** COMBIVIR should not be administered to pediatric
181 patients less than 12 years of age because it is a fixed-dose combination that cannot be adjusted
182 for this patient population.

183 **Gender: COMBIVIR:** A pharmacokinetic study in healthy male (n = 12) and female (n = 12)
184 subjects showed no gender differences in zidovudine exposure (AUC_{∞}) or lamivudine AUC_{∞}
185 normalized for body weight.

186 **Race: Lamivudine:** There are no significant racial differences in lamivudine
187 pharmacokinetics.

188 **Drug Interactions:** See PRECAUTIONS: Drug Interactions.

189 **COMBIVIR:** No drug interaction studies have been conducted using COMBIVIR Tablets.

190 **Lamivudine Plus Zidovudine:** No clinically significant alterations in lamivudine or
191 zidovudine pharmacokinetics were observed in 12 asymptomatic HIV-infected adult patients
192 given a single dose of zidovudine (200 mg) in combination with multiple doses of lamivudine
193 (300 mg q 12 hr).
194

195 **Table 2. Effect of Coadministered Drugs on Lamivudine and Zidovudine AUC***
 196 **Note: ROUTINE DOSE MODIFICATION OF LAMIVUDINE AND ZIDOVUDINE IS**
 197 **NOT WARRANTED WITH COADMINISTRATION OF THE FOLLOWING**
 198 **DRUGS.**

Drugs That May Alter Lamivudine Blood Concentrations					
Coadministered Drug and Dose	Lamivudine Dose	n	Lamivudine Concentrations		Concentration of Coadministered Drug
			AUC	Variability	
Nelfinavir 750 mg q 8 hr x 7 to 10 days	single 150 mg	11	↑AUC 10%	95% CI: 1% to 20%	↔
Trimethoprim 160 mg/ Sulfamethoxazole 800 mg daily x 5 days	single 300 mg	14	↑AUC 43%	90% CI: 32% to 55%	↔
Drugs That May Alter Zidovudine Blood Concentrations					
Coadministered Drug and Dose	Zidovudine Dose	n	Zidovudine Concentrations		Concentration of Coadministered Drug
			AUC	Variability	
Atovaquone 750 mg q 12 hr with food	200 mg q 8 hr	14	↑AUC 31%	Range 23% to 78%†	↔
Fluconazole 400 mg daily	200 mg q 8 hr	12	↑AUC 74%	95% CI: 54% to 98%	Not Reported
Methadone 30 to 90 mg daily	200 mg q 4 hr	9	↑AUC 43%	Range 16% to 64%†	↔
Nelfinavir 750 mg q 8 hr x 7 to 10 days	single 200 mg	11	↓AUC 35%	Range 28% to 41%	↔
Probenecid 500 mg q 6 hr x 2 days	2 mg/kg q 8 hr x 3 days	3	↑AUC 106%	Range 100% to 170%†	Not Assessed
Ritonavir 300 mg q 6 hr x 4 days	200 mg q 8 hr x 4 days	9	↓AUC 25%	95% CI: 15% to 34%	↔
Valproic acid 250 mg or 500 mg q 8 hr x 4 days	100 mg q 8 hr x 4 days	6	↑AUC 80%	Range 64% to 130%†	Not Assessed

199 ↑ = Increase; ↓ = Decrease; ↔ = no significant change; AUC = area under the concentration
 200 versus time curve; CI = confidence interval.

201 * This table is not all inclusive.

202 † Estimated range of percent difference.

203

204 **INDICATIONS AND USAGE**

205 **COMBIVIR in combination with other antiretroviral agents is indicated for the**
206 **treatment of HIV infection.**

207 **Description of Clinical Studies: COMBIVIR:** There have been no clinical trials conducted
208 with COMBIVIR. See CLINICAL PHARMACOLOGY for information about bioequivalence.
209 One COMBIVIR Tablet given twice daily is an alternative regimen to EPIVIR Tablets 150 mg
210 twice daily plus RETROVIR 600 mg per day in divided doses.

211 **Lamivudine Plus Zidovudine:** The NUCB3007 (CAESAR) study was conducted using
212 EPIVIR 150-mg Tablets (150 mg twice daily) and RETROVIR 100-mg Capsules (2 x 100 mg 3
213 times daily). CAESAR was a multicenter, double-blind, placebo-controlled study comparing
214 continued current therapy [zidovudine alone (62% of patients) or zidovudine with didanosine or
215 zalcitabine (38% of patients)] to the addition of EPIVIR or EPIVIR plus an investigational non-
216 nucleoside reverse transcriptase inhibitor, randomized 1:2:1. A total of 1,816 HIV-infected adults
217 with 25 to 250 (median 122) CD4 cells/mm³ at baseline were enrolled: median age was 36 years,
218 87% were male, 84% were nucleoside-experienced, and 16% were therapy-naive. The median
219 duration on study was 12 months. Results are summarized in Table 3.
220

221 **Table 3. Number of Patients (%) With At Least 1 HIV Disease-Progression Event or Death**

Endpoint	Current Therapy (n = 460)	EPIVIR plus Current Therapy (n = 896)	EPIVIR plus a NNRTI* plus Current Therapy (n = 460)
HIV progression or death	90 (19.6%)	86 (9.6%)	41 (8.9%)
Death	27 (5.9%)	23 (2.6%)	14 (3.0%)

222 *An investigational non-nucleoside reverse transcriptase inhibitor not approved in the United
223 States.

224 **CONTRAINDICATIONS**

225 COMBIVIR Tablets are contraindicated in patients with previously demonstrated clinically
226 significant hypersensitivity to any of the components of the product.

227 **WARNINGS**

228 COMBIVIR is a fixed-dose combination of lamivudine and zidovudine. Ordinarily,
229 COMBIVIR should not be administered concomitantly with lamivudine, zidovudine, or
230 TRIZIVIR[®], a fixed-dose combination of abacavir, lamivudine, and zidovudine.

231 The complete prescribing information for all agents being considered for use with
232 COMBIVIR should be consulted before combination therapy with COMBIVIR is initiated.

233 **Bone Marrow Suppression:** COMBIVIR should be used with caution in patients who have
234 bone marrow compromise evidenced by granulocyte count <1,000 cells/mm³ or hemoglobin
235 <9.5 g/dL (see ADVERSE REACTIONS).

236 Frequent blood counts are strongly recommended in patients with advanced HIV disease who
237 are treated with COMBIVIR. For HIV-infected individuals and patients with asymptomatic or
238 early HIV disease, periodic blood counts are recommended.

239 **Lactic Acidosis/Severe Hepatomegaly with Steatosis:** Lactic acidosis and severe
240 hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside

241 analogues alone or in combination, including lamivudine, zidovudine, and other antiretrovirals.
242 A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may
243 be risk factors. Particular caution should be exercised when administering COMBIVIR to any
244 patient with known risk factors for liver disease; however, cases have also been reported in
245 patients with no known risk factors. Treatment with COMBIVIR should be suspended in any
246 patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced
247 hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked
248 transaminase elevations).

249 **Myopathy:** Myopathy and myositis, with pathological changes similar to that produced by HIV
250 disease, have been associated with prolonged use of zidovudine, and therefore may occur with
251 therapy with COMBIVIR.

252 **Posttreatment Exacerbations of Hepatitis:** In clinical trials in non-HIV-infected patients
253 treated with lamivudine for chronic hepatitis B, clinical and laboratory evidence of exacerbations
254 of hepatitis have occurred after discontinuation of lamivudine. These exacerbations have been
255 detected primarily by serum ALT elevations in addition to re-emergence of hepatitis B viral
256 DNA (HBV DNA). Although most events appear to have been self-limited, fatalities have been
257 reported in some cases. Similar events have been reported from post-marketing experience after
258 changes from lamivudine-containing HIV treatment regimens to non-lamivudine-containing
259 regimens in patients infected with both HIV and HBV. The causal relationship to discontinuation
260 of lamivudine treatment is unknown. Patients should be closely monitored with both clinical and
261 laboratory follow-up for at least several months after stopping treatment. There is insufficient
262 evidence to determine whether re-initiation of lamivudine alters the course of posttreatment
263 exacerbations of hepatitis.

264 **PRECAUTIONS**

265 **Patients with HIV and Hepatitis B Virus Coinfection:** Safety and efficacy of lamivudine
266 have not been established for treatment of chronic hepatitis B in patients dually infected with
267 HIV and HBV. In non-HIV-infected patients treated with lamivudine for chronic hepatitis B,
268 emergence of lamivudine-resistant HBV has been detected and has been associated with
269 diminished treatment response (see EPIVIR-HBV package insert for additional information).
270 Emergence of hepatitis B virus variants associated with resistance to lamivudine has also been
271 reported in HIV-infected patients who have received lamivudine-containing antiretroviral
272 regimens in the presence of concurrent infection with hepatitis B virus. Posttreatment
273 exacerbations of hepatitis have also been reported (see WARNINGS).

274 **Patients with Impaired Renal Function:** Reduction of the dosages of lamivudine and
275 zidovudine is recommended for patients with impaired renal function. Patients with creatinine
276 clearance <50 mL/min should not receive COMBIVIR.

277 **Fat Redistribution:** Redistribution/accumulation of body fat including central obesity,
278 dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast
279 enlargement, and “cushingoid appearance” have been observed in patients receiving
280 antiretroviral therapy. The mechanism and long-term consequences of these events are currently
281 unknown. A causal relationship has not been established.

282 **Information for Patients:** COMBIVIR is not a cure for HIV infection and patients may
283 continue to experience illnesses associated with HIV infection, including opportunistic
284 infections. Patients should be advised that the use of COMBIVIR has not been shown to reduce
285 the risk of transmission of HIV to others through sexual contact or blood contamination. Patients

286 should be informed that the major toxicities of COMBIVIR are neutropenia and/or anemia. They
287 should be told of the extreme importance of having their blood counts followed closely while on
288 therapy, especially for patients with advanced HIV disease. Patients should be advised of the
289 importance of taking COMBIVIR as it is prescribed.

290 Patients should be informed that redistribution or accumulation of body fat may occur in
291 patients receiving antiretroviral therapy and that the cause and long-term health effects of these
292 conditions are not known at this time.

293 Patients co-infected with HIV and HBV should be informed that deterioration of liver disease
294 has occurred in some cases when treatment with lamivudine was discontinued. Patients should be
295 advised to discuss any changes in regimen with their physician.

296 **Drug Interactions: Lamivudine:** Trimethoprim (TMP) 160 mg/sulfamethoxazole (SMX)
297 800 mg once daily has been shown to increase lamivudine exposure (AUC). The effect of higher
298 doses of TMP/SMX on lamivudine pharmacokinetics has not been investigated (see CLINICAL
299 PHARMACOLOGY). No data are available regarding the potential for interactions with other
300 drugs that have renal clearance mechanisms similar to that of lamivudine.

301 Lamivudine and zalcitabine may inhibit the intracellular phosphorylation of one another.
302 Therefore, use of COMBIVIR in combination with zalcitabine is not recommended.

303 **Zidovudine:** Coadministration of ganciclovir, interferon-alpha, and other bone marrow
304 suppressive or cytotoxic agents may increase the hematologic toxicity of zidovudine.

305 Concomitant use of COMBIVIR with stavudine should be avoided since an antagonistic
306 relationship with zidovudine has been demonstrated in vitro. In addition, concomitant use of
307 zidovudine with doxorubicin or ribavirin should be avoided because an antagonistic relationship
308 has been demonstrated in vitro.

309 See CLINICAL PHARMACOLOGY for additional drug interactions.

310 **Carcinogenesis, Mutagenesis, and Impairment of Fertility: Carcinogenicity:**

311 **Lamivudine:** Long-term carcinogenicity studies with lamivudine in mice and rats showed
312 no evidence of carcinogenic potential at exposures up to 10 times (mice) and 58 times (rats)
313 those observed in humans at the recommended therapeutic dose for HIV infection.

314 **Zidovudine:** Zidovudine was administered orally at 3 dosage levels to separate groups of
315 mice and rats (60 females and 60 males in each group). Initial single daily doses were 30, 60, and
316 120 mg/kg/day in mice and 80, 220, and 600 mg/kg/day in rats. The doses in mice were reduced
317 to 20, 30, and 40 mg/kg/day after day 90 because of treatment-related anemia, whereas in rats
318 only the high dose was reduced to 450 mg/kg/day on day 91 and then to 300 mg/kg/day on
319 day 279.

320 In mice, 7 late-appearing (after 19 months) vaginal neoplasms (5 nonmetastasizing squamous
321 cell carcinomas, 1 squamous cell papilloma, and 1 squamous polyp) occurred in animals given
322 the highest dose. One late-appearing squamous cell papilloma occurred in the vagina of a
323 middle-dose animal. No vaginal tumors were found at the lowest dose.

324 In rats, 2 late-appearing (after 20 months), nonmetastasizing vaginal squamous cell
325 carcinomas occurred in animals given the highest dose. No vaginal tumors occurred at the low or
326 middle dose in rats. No other drug-related tumors were observed in either sex of either species.

327 At doses that produced tumors in mice and rats, the estimated drug exposure (as measured by
328 AUC) was approximately 3 times (mouse) and 24 times (rat) the estimated human exposure at
329 the recommended therapeutic dose of 100 mg every 4 hours.

330 Two transplacental carcinogenicity studies were conducted in mice. One study administered
331 zidovudine at doses of 20 mg/kg/day or 40 mg/kg/day from gestation day 10 through parturition

332 and lactation with dosing continuing in offspring for 24 months postnatally. The doses of
333 zidovudine employed in this study produced zidovudine exposures approximately 3 times the
334 estimated human exposure at recommended doses. After 24 months at the highest dose, an
335 increase in incidence of vaginal tumors was noted with no increase in tumors in the liver or lung
336 or any other organ in either gender. These findings are consistent with results of the standard oral
337 carcinogenicity study in mice, as described earlier. A second study administered zidovudine at
338 maximum tolerated doses of 12.5 mg/day or 25 mg/day (~1,000 mg/kg nonpregnant body weight
339 or ~450 mg/kg of term body weight) to pregnant mice from days 12 through 18 of gestation.
340 There was an increase in the number of tumors in the lung, liver, and female reproductive tracts
341 in the offspring of mice receiving the higher dose level of zidovudine.

342 It is not known how predictive the results of rodent carcinogenicity studies may be for
343 humans.

344 **Mutagenicity: Lamivudine:** Lamivudine was negative in a microbial mutagenicity screen,
345 in an in vitro cell transformation assay, in a rat micronucleus test, in a rat bone marrow
346 cytogenetic assay, and in an assay for unscheduled DNA synthesis in rat liver. It was mutagenic
347 in an L5178Y/TK^{+/-} mouse lymphoma assay and clastogenic in a cytogenetic assay using
348 cultured human lymphocytes.

349 **Zidovudine:** Zidovudine was mutagenic in an L5178Y/TK^{+/-} mouse lymphoma assay,
350 positive in an in vitro cell transformation assay, clastogenic in a cytogenetic assay using cultured
351 human lymphocytes, and positive in mouse and rat micronucleus tests after repeated doses. It
352 was negative in a cytogenetic study in rats given a single dose.

353 **Impairment of Fertility: Lamivudine:** In a study of reproductive performance,
354 lamivudine, administered to male and female rats at doses up to 130 times the usual adult dose
355 based on body surface area considerations, revealed no evidence of impaired fertility (judged by
356 conception rates) and no effect on the survival, growth, and development to weaning of the
357 offspring.

358 **Zidovudine:** Zidovudine, administered to male and female rats at doses up to 7 times the
359 usual adult dose based on body surface area considerations, had no effect on fertility judged by
360 conception rates.

361 **Pregnancy:** Pregnancy Category C.

362 **COMBIVIR:** There are no adequate and well-controlled studies of COMBIVIR in pregnant
363 women. Reproduction studies with lamivudine and zidovudine have been performed in animals
364 (see Lamivudine and Zidovudine sections below). COMBIVIR should be used during pregnancy
365 only if the potential benefits outweigh the risks.

366 **Lamivudine:** Reproduction studies with orally administered lamivudine have been
367 performed in rats and rabbits at doses up to 4,000 mg/kg/day and 1,000 mg/kg/day, respectively,
368 producing plasma levels up to approximately 35 times that for the adult HIV dose. No evidence
369 of teratogenicity due to lamivudine was observed. Evidence of early embryoletality was seen in
370 the rabbit at exposure levels similar to those observed in humans, but there was no indication of
371 this effect in the rat at exposure levels up to 35 times that in humans. Studies in pregnant rats and
372 rabbits showed that lamivudine is transferred to the fetus through the placenta.

373 **Zidovudine:** Reproduction studies with orally administered zidovudine in the rat and in the
374 rabbit at doses up to 500 mg/kg/day revealed no evidence of teratogenicity with zidovudine.
375 Zidovudine treatment resulted in embryo/fetal toxicity as evidenced by an increase in the
376 incidence of fetal resorptions in rats given 150 or 450 mg/kg/day and rabbits given

377 500 mg/kg/day. The doses used in the teratology studies resulted in peak zidovudine plasma
378 concentrations (after one half of the daily dose) in rats 66 to 226 times, and in rabbits 12 to
379 87 times, mean steady-state peak human plasma concentrations (after one sixth of the daily dose)
380 achieved with the recommended daily dose (100 mg every 4 hours). In an additional teratology
381 study in rats, a dose of 3,000 mg/kg/day (very near the oral median lethal dose in rats of
382 3,683 mg/kg) caused marked maternal toxicity and an increase in the incidence of fetal
383 malformations. This dose resulted in peak zidovudine plasma concentrations 350 times peak
384 human plasma concentrations. No evidence of teratogenicity was seen in this experiment at doses
385 of 600 mg/kg/day or less. Two rodent carcinogenicity studies were conducted (see
386 Carcinogenesis, Mutagenesis, Impairment of Fertility).

387 **Antiretroviral Pregnancy Registry:** To monitor maternal-fetal outcomes of pregnant
388 women exposed to COMBIVIR and other antiretroviral agents, an Antiretroviral Pregnancy
389 Registry has been established. Physicians are encouraged to register patients by calling 1-800-
390 258-4263.

391 **Nursing Mothers: The Centers for Disease Control and Prevention recommend that**
392 **HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission**
393 **of HIV infection.** No specific studies of lamivudine and zidovudine excretion in breast milk
394 after dosing with COMBIVIR have been performed. Zidovudine and lamivudine are excreted in
395 human breast milk (see CLINICAL PHARMACOLOGY: Pharmacokinetics: Nursing Mothers).
396 A study in lactating rats administered 45 mg/kg of lamivudine showed that lamivudine
397 concentrations in milk were slightly greater than those in plasma.

398 Because of both the potential for HIV transmission and the potential for serious adverse
399 reactions in nursing infants, **mothers should be instructed not to breastfeed if they are**
400 **receiving COMBIVIR.**

401 **Pediatric Use:** COMBIVIR should not be administered to pediatric patients less than 12 years
402 of age because it is a fixed-dose combination that cannot be adjusted for this patient population.

403 **Geriatric Use:** Clinical studies of COMBIVIR did not include sufficient numbers of subjects
404 aged 65 and over to determine whether they respond differently from younger subjects. In
405 general, dose selection for an elderly patient should be cautious, reflecting the greater frequency
406 of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug
407 therapy. COMBIVIR is not recommended for patients with impaired renal function (i.e.,
408 creatinine clearance <50 mL/min; see PRECAUTIONS: Patients with Impaired Renal Function
409 and DOSAGE AND ADMINISTRATION).

410 **ADVERSE REACTIONS**

411 **Lamivudine Plus Zidovudine Administered As Separate Formulations:** In
412 4 randomized, controlled trials of EPIVIR 300 mg per day plus RETROVIR 600 mg per day, the
413 following selected clinical and laboratory adverse events were observed (see Tables 4 and 5).

414

415 **Table 4. Selected Clinical Adverse Events (≥5% Frequency) in 4 Controlled Clinical Trials**
 416 **With EPIVIR 300 mg/day and RETROVIR 600 mg/day**

Adverse Event	EPIVIR plus RETROVIR (n = 251)
Body as a whole Headache Malaise & fatigue Fever or chills	35% 27% 10%
Digestive Nausea Diarrhea Nausea & vomiting Anorexia and/or decreased appetite Abdominal pain Abdominal cramps Dyspepsia	33% 18% 13% 10% 9% 6% 5%
Nervous system Neuropathy Insomnia & other sleep disorders Dizziness Depressive disorders	12% 11% 10% 9%
Respiratory Nasal signs & symptoms Cough	20% 18%
Skin Skin rashes	9%
Musculoskeletal Musculoskeletal pain Myalgia Arthralgia	12% 8% 5%

417
 418 Pancreatitis was observed in 3 of the 656 adult patients (<0.5%) who received EPIVIR in
 419 controlled clinical trials.

420 Selected laboratory abnormalities observed during therapy are listed in Table 5.

421

422 **Table 5. Frequencies of Selected Laboratory Abnormalities Among Adults in 4 Controlled**
 423 **Clinical Trials of EPIVIR 300 mg/day plus RETROVIR 600 mg/day***

Test (Abnormal Level)	EPIVIR plus RETROVIR % (n)
Neutropenia (ANC<750/mm ³)	7.2% (237)
Anemia (Hgb<8.0 g/dL)	2.9% (241)
Thrombocytopenia (platelets<50,000/mm ³)	0.4% (240)
ALT (>5.0 x ULN)	3.7% (241)
AST (>5.0 x ULN)	1.7% (241)
Bilirubin (>2.5 x ULN)	0.8% (241)
Amylase (>2.0 x ULN)	4.2% (72)

424 ULN = Upper limit of normal.

425 ANC = Absolute neutrophil count.

426 n = Number of patients assessed.

427 *Frequencies of these laboratory abnormalities were higher in patients with mild laboratory
 428 abnormalities at baseline.

429

430 **Observed During Clinical Practice:** In addition to adverse events reported from clinical
 431 trials, the following events have been identified during post-approval use of EPIVIR,
 432 RETROVIR, and/or COMBIVIR. Because they are reported voluntarily from a population of
 433 unknown size, estimates of frequency cannot be made. These events have been chosen for
 434 inclusion due to a combination of their seriousness, frequency of reporting, or potential causal
 435 connection to EPIVIR, RETROVIR, and/or COMBIVIR.

436 **Body as a Whole:** Redistribution/accumulation of body fat (see PRECAUTIONS: Fat
 437 Redistribution).

438 **Cardiovascular:** Cardiomyopathy.

439 **Endocrine and Metabolic:** Gynecomastia, hyperglycemia.

440 **Gastrointestinal:** Oral mucosal pigmentation, stomatitis.

441 **General:** Vasculitis, weakness.

442 **Hemic and Lymphatic:** Anemia, (including pure red cell aplasia and anemias progressing
 443 on therapy), lymphadenopathy, splenomegaly.

444 **Hepatic and Pancreatic:** Lactic acidosis and hepatic steatosis, pancreatitis, posttreatment
 445 exacerbation of hepatitis B (see WARNINGS).

446 **Hypersensitivity:** Sensitization reactions (including anaphylaxis), urticaria.

447 **Musculoskeletal:** Muscle weakness, CPK elevation, rhabdomyolysis.

448 **Nervous:** Paresthesia, peripheral neuropathy, seizures.

449 **Respiratory:** Abnormal breath sounds/wheezing.

450 **Skin:** Alopecia, erythema multiforme, Stevens-Johnson syndrome.

451 **OVERDOSAGE**

452 **COMBIVIR:** There is no known antidote for COMBIVIR.

453 **Lamivudine:** One case of an adult ingesting 6 grams of lamivudine was reported; there were no
454 clinical signs or symptoms noted and hematologic tests remained normal. It is not known
455 whether lamivudine can be removed by peritoneal dialysis or hemodialysis.

456 **Zidovudine:** Acute overdoses of zidovudine have been reported in pediatric patients and adults.
457 These involved exposures up to 50 grams. The only consistent findings were nausea and
458 vomiting. Other reported occurrences included headache, dizziness, drowsiness, lethargy,
459 confusion, and 1 report of a grand mal seizure. Hematologic changes were transient. All patients
460 recovered. Hemodialysis and peritoneal dialysis appear to have a negligible effect on the removal
461 of zidovudine, while elimination of its primary metabolite, GZDV, is enhanced.

462 **DOSAGE AND ADMINISTRATION**

463 The recommended oral dose of COMBIVIR for adults and adolescents (at least 12 years of
464 age) is 1 tablet (containing 150 mg of lamivudine and 300 mg of zidovudine) twice daily.

465 **Dose Adjustment:** Because it is a fixed-dose combination, COMBIVIR should not be
466 prescribed for patients requiring dosage adjustment such as those with reduced renal function
467 (creatinine clearance <50 mL/min) or those experiencing dose-limiting adverse events.

468 A reduction in the daily dose of zidovudine may be necessary in patients with mild to
469 moderate impaired hepatic function or liver cirrhosis. Because COMBIVIR is a fixed-dose
470 combination that cannot be adjusted for this patient population, COMBIVIR is not recommended
471 for patients with impaired hepatic function.

472 **HOW SUPPLIED**

473 COMBIVIR Tablets, containing 150 mg lamivudine and 300 mg zidovudine, are white,
474 film-coated, modified-capsule-shaped tablets engraved with “GXFC3” on one side. They are
475 available as follows:

476 60 Tablets/Bottle (NDC 0173-0595-00)

477 **Store between 2° and 30°C (36° and 86°F).**

478 Unit Dose Pack of 120 (NDC 0173-0595-02)

479 **Store between 2° and 30°C (36° and 86°F).**

480

481



482 **GlaxoSmithKline**

483

483 GlaxoSmithKline

484 Research Triangle Park, NC 27709

485

486 Lamivudine is manufactured under agreement from

487 **Shire Pharmaceuticals Group plc**

488 Basingstoke, UK

489

490 ©2004, GlaxoSmithKline. All rights reserved.

491

492 ~~April~~ **May** 2004

RL-20882073 |